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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 148 049 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
15.12.2004 Bulletin 2004/51

(51) Int Cl.[7]: **C07D 207/34**, A61K 31/40

(21) Application number: **01116338.3**

(22) Date of filing: **08.07.1996**

(54) **Crystalline R-(R*,R*)$-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-(phenylamino)carbonyl -1H-pyrrole-1-heptanoic acid hemi calcium salt (atorvastatin)**

Kristaline (R-(R*,R*))-2-(4-Fluorphenyl)-Beta,Delta-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-((Phenylamino)Carbonyl)-1H-Pyrrol-1-Heptancarbonsäure Hemi Calcium Sslz (Atorvastatin)

Formes cristallines d'hémi-sel de calcium d'acide r-(r*,r*)]-2-(4-fluorophényl)-beta,delta-dihydroxy-5-(1-methyléthyl)-3-phényl-4-(phenylamino)carbonyl]-1h-pyrrole-1-heptanoique (atorvastatine)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
LT LV SI

(30) Priority: **17.07.1995 US 1452 P**

(43) Date of publication of application:
24.10.2001 Bulletin 2001/43

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
96924368.2 / 0 848 705

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(56) References cited:
EP-A- 0 409 281 **WO-A-94/16693**

- **BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039**

EP 1 148 049 B1

Description

BACKGROUND OF THE INVENTION

[0001] The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are thus useful hypolipidemic and hypocholesterolemic agents.

[0002] United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans (±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

[0003] United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

[0004] United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

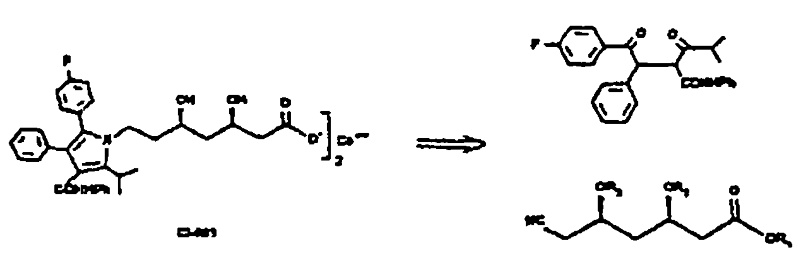
[0005] Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

[0006] Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

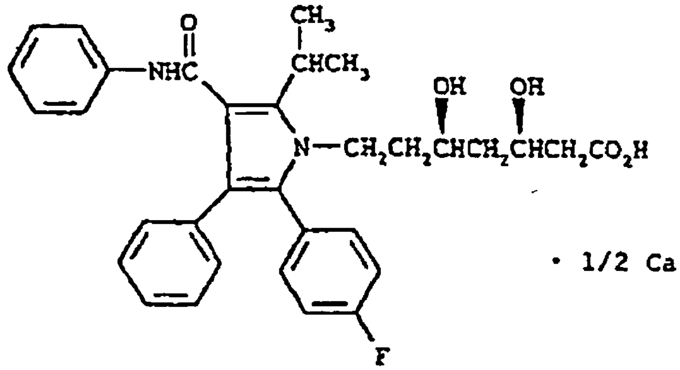
[0007] The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

[0008] EP-A-0 409 281 discloses [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; a process for their preparation and pharmaceutically acceptable salts thereof.

[0009] Tetrahedron Letters, Vol. 33, No. 17, pp. 2283-2284, 1992, Baumann, Kelvin et al. describe the synthesis of CI-981 and the key chiral intermediate (2):



[0010] WO-A-94/16693 discloses an oral pharmaceutical composition for treating hypercholesterolemia or hyperlipidemia containing an advantageous formulation for stabilizing the HMG-CoA coenzyme A inhibitor, CI-981 Hemi-Calcium, of formula (IA) with effective amounts of calcium carbonate.



(IA)

[0011] We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in new crystalline forms designated Form II, and Form IV

SUMMARY OF THE INVENTION

[0012] Accordingly, the present invention is directed to

1. Crystalline Form II atorvastatin (i.e. (R- (R*, R*)]-2-(4-fluorophenyl) -β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 8.533 and 9.040;

2. Crystalline Form II atorvastatin hydrate according to item 1, wherein the X-ray powder diffraction pattern further contains the following 2θ values measured using CuK_α radiation: 17.120 - 17.360 (broad) and 20.502;

3. Crystalline Form II atorvastatin hydrate according to item 2, wherein the X-ray powder diffraction pattern further contains the following 2θ values measured using CuK_α radiation: 5.582, 7.384, 19.490 and 22.706 - 23.159 (broad);

4. Crystalline Form II atorvastatin hydrate having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120 - 17.360 (broad), 19.490, 20.502, 22.706 - 23.159 (broad) 25.697 (broad) and 29.504;

5. Crystalline Form II atorvastatin hydrate having an X-ray powder diffraction pattern containing at least one of the following 2θ values measured using CuK_α radiation: 9.040 or 20.502;

6. Crystalline Form II atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expresseed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad) ;

7. Crystalline Form IV atorvastatin (i.e. [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 7.997 and 9.680;

8. Crystalline Form IV atorvastatin hydrate according to item 7, wherein the X-ray powder diffraction pattern further contains the following 2θ value measured using CuK_α radiation: 19.569;

9. Crystalline Form IV atorvastatin hydrate having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 4.889, 5.424, 5.940, 7.997, 9.680, 10.416, 12.355, 17.662, 18.367, 19.200, 19.569, 21.723, 23.021, 23.651 and 24.143;

10. Crystalline Form IV atorvastatin hydrate having an X-ray powder diffraction pattern containing at least one of the following 2θ values measured using CuK_α radiation: 7.997 or 9.680;

11. Crystalline Form IV atorvastatin hydrate characterized by solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1, 129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4;

12. A pharmaceutical composition comprising crystalline Form II or Form IV atorvastatin hydrate according to any one of the preceding items in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier;

13. A pharmaceutical composition according to item 12 in the form of tablets, pills, dispersible granules, cachets, capsules, powders, lozenges, suppositories or retention enemas; and

14. Use of crystalline Form II or Form IV atorvastatin hydrate according to any one of items 1 to 11 in the medicine.

[0013] As inhibitors of HMG-CoA, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 to 4, short particulars of which are given below.

Figure 1
Diffractogram of Form II atorvastatin hydrate ground for 2 minutes (Y-axis = 0 to maximum intensity of 1500 counts per second (cps)).

Figure 2
Diffractogram of Form IV atorvastatin hydrate (Y-axis = 0 to maximum intensity of 8212.5 cps).

Figure 3
Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form II atorvastatin hydrate.

Figure 4
Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form IV atorvastatin hydrate.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Crystalline Form II, or Form IV atorvastatin hydrate may be characterized by their X-ray powder diffraction patterns and/or by their solid state nuclear magnetic resonance spectra (NMR).

X-RAY POWDER DIFFRACTION

Forms II, and IV Atorvastatin Hydrate

[0016] Forms II, or Form IV atorvastatin hydrate were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms II, and Form IV atorvastatin hydrate were measured on a Siemens D-500 diffractometer with CuK_a radiation.

Equipment

[0017] Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).
[0018] CuK_a radiation (20 mA, 40 kV, λ = 1.5406 Å) slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)]Detector (Slits: III at 1° and IV at 0.15°).

Methodology

[0019] The silicon standard is run each day to check the X-ray tube alignment.
[0020] Continuous θ/2θ coupled scan: 4.00° to 40.00° in 2θ, scan rate of 6°/min: 0.4 sec/0.04° step.
[0021] Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13-15 mm.
[0022] Samples are stored and run at room temperature.

Grinding/Sieving

[0023] Grinding is used to minimize intensity variations for the diffractogram disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.
[0024] Ground Form II atorvastatin hydrate was sieved through a 230 mesh screen before analysis by x-ray diffraction.
[0025] Table 1 lists the 2θ, d-spacings, and relative intensities of all lines in the ground/sieved sample with a relative intensity of >20% for crystalline Form II atorvastatin hydrate. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 1.

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 20% for Form II Atorvastatin hydrate		
2θ	d	Relative Intensity (>20%)
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

[0026] Table 2 lists the 2θ, d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >15% for crystalline Form IV atorvastatin hydrate. It should also be noted that the computer-generated unrounded numbers are listed in this table.

TABLE 2.

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 15% for Form IV Atorvastatin hydrate		
2θ	d	Relative Intensity (>15%)
4.889	18.605	38.45
5.424	16.2804	20.12
5.940	14.8660	17.29
7.997	11.0465	100.00
9.680	9.1295	67.31
10.416	8.4859	20.00
12.355	7.1584	19.15
17.662	5.0175	18.57

TABLE 2. (continued)

Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 15% for Form IV Atorvastatin hydrate		
2θ	d	Relative Intensity (>15%)
18.367	4.8265	23.50
19.200	4.6189	18.14
19.569	4.5327	54.79
21.723	4.0879	17.99
23.021	3.8602	28.99
23.651	3.7587	33.39
24.143	3.6832	17.23

SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

[0027] All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988; 76:54).

[0028] Table 3 shows the solid-state NMR spectrum for crystalline Form II atorvastatin hydrate.

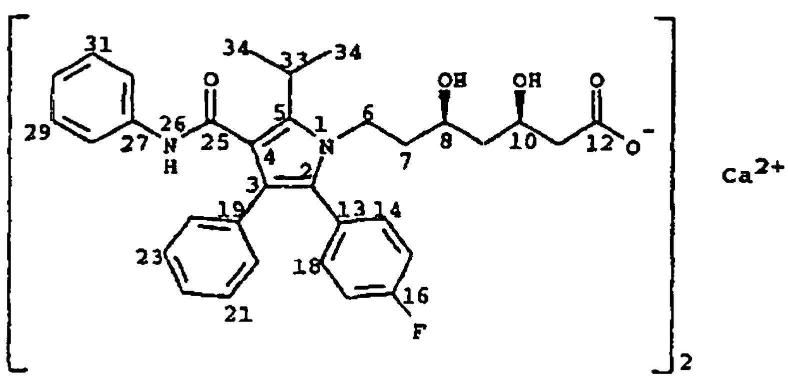


TABLE 3.

Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin hydrate	
Assignment	Chemical Shift
Spinning Side Band	209.1
Spinning Side Band	206.8
C12 or C25	181 (broad)
C12 or C25	163 (broad)
C16	161 (broad)
Aromatic Carbons	

TABLE 3. (continued)

Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin hydrate	
Assignment	Chemical Shift
C2-C5, C13-C18, C19-C24, C27-C32	140.5 134.8 133.3 129.0 122.9 121.4 120.3 119.0 117.1 115.7 114.7 70.6 69.0
C8, C10	68.0 67.3
Spinning Side Band	49.4
Spinning Side Band	48.9
Methylene Carbons C6, C7, C9, C11	 43.4 42.3 41.7 40.2
C33	27.5
C34	22.8 (broad)

[0029] Table 4 shows the solid-state NMR spectrum for crystalline Form IV atorvastatin hydrate.

TABLE 4.

Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin hydrate	
Assignment	Chemical Shift
C12 or C25	186.4 184.9
C12 or C25	181.4 179.3
C16	166.1 (broad) and 159.0 (broad)
Aromatic Carbons C2-C5, C13-C18, C19-C24, C27-C32	 138.1 (broad) 134.7 129.2 127.1 122.7 119.8 115.7

TABLE 4. (continued)

Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin hydrate	
Assignment	Chemical Shift
C8,C10	71.5 67.5 66.3 63.5
Methylene Carbons C6, C7, C9, C11	46.1 43.4 42.1 40.0
C33	25.9
C34	20.3 19.4 17.9

[0030] Crystalline Form II, and Form IV atorvastatin hydrate of the present invention exist in hydrated forms.

[0031] EP 0 848 705 B1 describes a process for the preparation of crystalline From I atorvastatin hydrate which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin hydrate.

[0032] The precise conditions under which crystalline Form I atorvastatin hydrate is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

[0033] Thus, for example, crystalline Form I atorvastatin hydrate may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example, methanol and the like, is preferred.

[0034] When the starting material for the preparation of the desired crystalline Form I atorvastatin hydrate is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70°C such as, for example, about 45-60°C, particularly preferred about 47-52°C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, the calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature, for example within the above-mentioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl tert-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin hydrate to the crystallization solution in order to consistently produce crystalline Form I atorvastatin hydrate.

[0035] When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I atorvastatin hydrate, the desired crystalline Form I atorvastatin hydrate may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin hydrate to the suspension in order to ensure complete conversion to crystalline Form I atorvastatinhydrate. Alternatively, a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75°C, particularly preferred about 65-70°C, until a significant amount of crystalline Form I atorvastatin hydrate is present, whereupon the amorphous/crystalline Form I mixture can be slurried as described above.

[0036] Crystalline form I atorvastatin hydrate is significantly easier to isolate than amorphous atorvastatin and can be filtered from the crystallization medium after cooling, and washed and dried. For example, filtration of a 50 mL slurry of crystalline Form I atorvastatin hydrate was complete within 10 seconds. A similarly sized sample of amorphous atorvastatin took more than an hour to filter.

[0037] The present invention provides a process for the preparation of crystalline Form II atorvastatin hydrate which comprises suspending atorvastatin in solvents under conditions which yield crystalline Form II atorvastatin hydrate.
[0038] The precise conditions under which crystalline Form II atorvastatin hydrate is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice.
[0039] Thus, for example, when the starting material is amorphous, a combination of amorphous and Form I, or crystalline Form I atorvastatin hydrate, the desired crystalline Form II atorvastatin hydrate may be obtained by suspending the solid in methanol containing about 40% to about 50% water until conversion to the required form is complete, followed by filtration.
[0040] The present invention also provides a process for the preparation of crystalline Form IV atorvastatin hydrate which comprises crystallizing atorvastatin from a solution thereof in solvents under conditions which yield crystalline Form IV atorvastatin hydrate.
[0041] The precise conditions under which crystalline Form IV atorvastatin hydrate is formed may be empirically determined and it is only possible to give a method which has been found to be suitable in practice.
[0042] Thus, for example, when the starting material is crystalline Form I atorvastatin hydrate, the desired crystalline Form IV atorvastatin hydrate may be obtained by dissolving the solid in methanol whereupon crystalline Form IV atorvastatin hydrate precipitates.
[0043] The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.
[0044] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.
[0045] In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.
[0046] In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.
[0047] The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.
[0048] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.
[0049] Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.
[0050] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.
[0051] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.
[0052] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.
[0053] The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0054] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0055] In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Forms II, and IV atorvastatin hydrate utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[0056] The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1 (does not fall within the scope of the present invention)

[R-(R*,R*)]-2-(4-Fluorophenyl)-β,δ-dihydroxy-5- (1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin hydrate)

Method A

[0057] A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin hydrate (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin hydrate (72.2 kg).

Method B

[0058] Amorphous atorvastatin (9 g) and crystalline Form I atorvastatinhydrate (1 g) are stirred at about 40°C in a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70°C under reduced pressure to give crystalline Form I atorvastatin hydrate (9.7 g).

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin hydrate)

[0059] A mixture of amorphous and crystalline Form I atorvastatin hydrate (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II atorvastatin hydrate.

EXAMPLE 3

[R-(R*,R*)]-2- (4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form IV Atorvastatin hydrate)

[0060] A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995)(12 kg), MTBE (50 kg), methanol (30 L) is reacted with an aqueous solution of sodium hydroxide (1.83 kg in 150 L) at 50-55°C for 30-45 minutes to form the ring-opened sodium salt. After cooling to 20-25°C, the organic layer is discarded

and the aqueous layer is again extracted with MTBE (37 kg). The organic layer is discarded and the aqueous solution of the sodium salt is heated to 70-80°C and the residual MTBE is removed by distillation. The solution is then cooled to 60-70°C. To this solution is added a solution of calcium acetate hemihydrate (1.91 kg) dissolved in water/methanol (72 L water + 16 L methanol). The mixture is seeded with crystalline Form I atorvastatin hydrate (180 g) shortly after addition of the calcium acetate solution. The mixture is heated at 65-75°C for at least 5 minutes and then cooled to 50-55°C. The mixture is filtered and slurried in methanol (about 200 L) at 55-65°C and then cooled to 25-30°C and filtered. The solid is dried at (66-70°C under vacuum to give Form IV of crystalline atorvastatin hydrate (about 3 kg isolated).

Claims

1. Crystalline Form II atorvastatin (i.e. [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 8.533 and 9.040.

2. Crystalline Form II atorvastatin hydrate according to claim 1, wherein the X-ray powder diffraction pattern further contains the following 2θ values measured using CuK_α radiation: 17.120 - 17.360 (broad) and 20.502.

3. Crystalline Form II atorvastatin hydrate according to claim 2, wherein the X-ray powder diffraction pattern further contains the following 2θ values measured using CuK_α radiation: 5.582, 7.384, 19.490 and 22.706 - 23.159 (broad).

4. Crystalline Form II atorvastatin hydrate having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120-17.360 (broad), 19.490, 20.502, 22.706 - 23.159 (broad) 25.697 (broad) and 29.504.

5. Crystalline Form II atorvastatin hydrate having an X-ray powder diffraction pattern containing at least one of the following 2θ values measured using CuK_α radiation: 9.040 or 20.502.

6. Crystalline Form II atorvastatin hydrate **characterized by** solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expresseed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

7. Crystalline Form IV atorvastatin (i.e. [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following 29 values measured using CuK_α radiation: 7.997 and 9.680.

8. Crystalline Form IV atorvastatin hydrate according to claim 7, wherein the X-ray powder diffraction pattern further contains the following 2θ value measured using CuK_α radiation: 19.569.

9. Crystalline Form IV atorvastatin hydrate having an X-ray powder diffraction pattern containing the following 2θ values measured using CuK_α radiation: 4.889, 5.424, 5.940, 7.997, 9.680, 10.416, 12.355, 17.662, 18.367, 19.200, 19.569, 21.723, 23.021, 23.651 and 24.143.

10. Crystalline Form IV atorvastatin hydrate having an X-ray powder diffraction pattern containing at least one of the following 2θ values measured using CuK_α radiation: 7.997 or 9.680.

11. Crystalline Form IV atorvastatin hydrate **characterized by** solid-state ^{13}C nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1, 129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.

12. A pharmaceutical composition comprising crystalline Form II or Form IV atorvastatin hydrate according to any one of the preceding claims in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier.

13. A pharmaceutical composition according to claim 12 in the form of tablets, pills, dispersible granules, cachets, capsules, powders, lozenges, suppositories or retention enemas.

14. Use of crystalline Form II or Form IV atorvastatin hydrate according to any one of claims 1 to 11 in the medicine.

Patentansprüche

1. Kristallines Atorvastatin (d.h. [R-(R*,R*)]-2-(4-Fluorphenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-heptansäure-hemicalciumsalz)-Hydrat der Form II mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2θ-Werte enthält: 8,533 und 9,040.

2. Kristallines Atorvastatinhydrat der Form II gemäß Anspruch 1, wobei das Pulverröntgenbeugungsmuster ferner die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2Θ -Werte enthält: 17,120-17,360 (breit) und 20,502.

3. Kristallines Atorvastatinhydrat der Form II gemäß Anspruch 2, wobei das Pulverröntgenbeugungsmuster ferner die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2Θ -Werte enthält: 5,582, 7,384, 19,490 und 22,706-23,159 (breit).

4. Kristallines Atorvastatinhydrat der Form II mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2Θ -Werte enthält: 5,582, 7,384, 8,533, 9,040, 12,440 (breit), 15,771 (breit), 17,120-17,360 (breit), 19,490, 20,502, 22,706-23,159 (breit), 25,697 (breit) und 29,504.

5. Kristallines Atorvastatinhydrat der Form II mit einem Pulverröntgenbeugungsmuster, das mindestens einen der im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2Θ-Werte enthält: 9,040 oder 20,502.

6. Kristallines Atorvastatinhydrat der Form II, charakterisiert durch Festkörper-^{13}C-Kernresonanz mit den im folgenden angegebenen chemischen Verschiebungen in ppm (parts per million): 22,8 (breit), 27,5, 40,2, 41,7, 42,3, 43,4, 67,3, 68,0, 69,0, 70,6, 114,7, 115,7, 117,1, 119,0, 120,3, 121,4, 122,9, 129,0, 133,3, 134,8, 140,5, 161 (breit), 163 (breit) und 181 (breit).

7. Kristallines Atorvastatin (d.h. [R-(R*,R*)]-2-(4-Fluorphenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrol-1-heptansäure-hemicalciumsalz)-Hydrat der Form IV mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2θ-Werte enthält: 7,997 und 9,680.

8. Kristallines Atorvastatinhydrat der Form IV gemäß Anspruch 7, wobei das Pulverröntgenbeugungsmuster ferner den folgenden, unter Verwendung von CuK_α-Strahlung ermittelten 2θ-Wert 19,569 enthält.

9. Kristallines Atorvastatinhydrat der Form IV mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2θ-Werte enthält: 4,889, 5,424, 5,940, 7,997, 9,680, 10,416, 12,355, 17,662, 18,367, 19,200, 19,569, 21,723, 23,021, 23,651 und 24,143.

10. Kristallines Atorvastatinhydrat der Form IV mit einem Pulverröntgenbeugungsmuster, das mindestens einen der im folgenden angegebenen, unter Verwendung von CuK_α-Strahlung ermittelten 2Θ -Werte enthält: 7,997 oder 9,680.

11. Kristallines Atorvastatinhydrat der Form IV, charakterisiert durch Festkörper-^{13}C-Kernresonanz mit den im folgenden angegebenen chemischen Verschiebungen in ppm (parts per million): 17,9, 19,4, 20,3, 25,9, 40,0, 42,1, 43,4, 46,1, 63,5, 66,3, 67,9, 71,5, 115,7, 119,8, 122,7, 127,1, 129,2, 134,7, 138,1 (breit), 159,0 (breit), 166,1 (breit), 179,3, 181,4, 184,9 und 186,4.

12. Pharmazeutische Zusammensetzung, die kristallines Atorvastatinhydrat der Form II oder der Form IV gemäß einem der vorhergehenden Ansprüche im Gemisch mit mindestens einem pharmazeutisch akzeptablen Streckmittel, Verdünnungsmittel oder Träger enthält.

13. Pharmazeutische Zusammensetzung gemäß Anspruch 12 in Form von Tabletten, Pillen, dispergierbaren Granulatkörnchen, Kachets, Kapseln, Pulvern, Pastillen, Suppositorien oder Retentionsklistieren.

14. Verwendung kristallinem Atorvastatinhydrat der Form II oder der Form IV gemäß einem der Ansprüche 1-11 in der Medizin.

Revendications

1. La forme cristalline II d'hydrate d'atorvastatine (c'est-à-dire l'hydrate de l'hémisel calcique de l'acide [R-(R*,R*)]-2-(4-fluorophényl)-β,δ-dihydroxy-5-(1-méthyléthyl)-3-phényl-4-[(phénylamino)-carbonyl]-1H-pyrrole-1-heptanoïque), ayant un diagramme de diffraction de poudres aux rayons X présentant les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 8,533 et 9,040

2. La forme cristalline II d'hydrate d'atorvastatine suivant la revendication 1, où le diagramme de diffraction de poudres aux rayons X présente en outre les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 17,120 - 17,360 (large) et 20,502.

3. La forme cristalline II d'hydrate d'atorvastatine selon la revendication 2, où le diagramme de diffraction de poudres aux rayons X présente en outre les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 5,582, 7,384, 19,490, et 22,706 - 23,159 (large).

4. La forme cristalline II d'hydrate d'atorvastatine ayant un diagramme de diffraction de poudres aux rayons X présentant les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 5,582; 7,384; 8,533; 9,040; 12,440 (large); 15,771 (large); 17,120 - 17,360 (large); 19,490; 20,502; 22,706 - 23,159 (large); 25,697 (large); et 29,504.

5. La forme cristalline II d'hydrate d'atorvastatine ayant un diagramme de diffraction de poudres aux rayons X présentant au moins l'une des valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 9,040 ou 20,502.

6. La forme cristalline II d'hydrate d'atorvastatine, **caractérisé par** une résonance magnétique nucléaire de ^{13}C à l'état solide présentant les déplacements chimiques suivants, exprimés en parties par million: 22,8 (large); 27,5; 40,2; 41,7; 42,3; 43,4; 67,3; 68,0; 69,0; 70,6; 114,7; 115,7; 117,1; 119,0; 120,3; 121,4; 122,9; 129,0; 133,3; 134,8; 140,5; 161 (large); 163 (large) et 181 (large);

7. La forme cristalline IV d'hydrate d'atorvastatine (c'est-à-dire l'hydrate de l'hémisel calcique de l'acide de [R-(R*, R*)]-2-(4-fluorophényl)-β,δ-dihydroxy-5-(1-méthyléthyl)-3-phényl-4-[(phénylamino)-carbonyl]-1H-pyrrole-1-heptanoïque), ayant un diagramme de diffraction de poudres aux rayons X présentant les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 7,997 et 9,680.

8. La forme cristalline IV d'hydrate d'atorvastatine selon la revendication 7, où le diagramme de diffraction de poudres aux rayons X présente en outre les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 19,569.

9. La forme cristalline IV d'hydrate d'atorvastatine, où le diagramme de diffraction de poudres aux rayons X présente les valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 4,889; 5,424; 5,940; 7,997; 9,680; 10,416, 12,335; 17,662; 18,367; 19,200; 19,569; 21,723. 23,021; 23,651 et 24,143.

10. La forme cristalline IV d'hydrate d'atorvastatine ayant un diagramme de diffraction de poudres aux rayons X contenant au moins l'une des valeurs 2θ suivantes mesurées avec la raie K_α du cuivre: 7,997 ou 9,680.

11. La forme cristalline IV d'hydrate d'atorvastatine, **caractérisée par** une résonance magnétique nucléaire de ^{13}C à l'état solide présentant les déplacements chimiques suivants, exprimés en parties par million: 17,9; 19,4; 20,3; 25,9; 40,0; 42,1; 43,4; 46,1; 63,5; 66,3; 67,9; 71,5; 115,7; 119,8; 122,7; 127,1; 129,2; 134,7; 138,1 (large); 159,0 (large); 166,1 (large); 179,3; 181,4; 184,9 et 186,4.

12. Une composition pharmaceutique comprenant la forme cristalline II ou la forme cristalline IV d'hydrate d'atorvastatine selon l'une quelconque des revendications précédentes en mélange avec au moins un excipient, diluant ou support acceptable du point de vue pharmaceutique.

13. Une composition pharmaceutique selon la revendication 12, sous forme de comprimés, de pilules, de granulés pouvant être dispersés, de cachets, de gélules, de poudres, de pastilles, de suppositoires ou de lavements à garder.

14. L'utilisation en médecine d'un hydrate d'atorvastatine sous la forme cristalline II ou la forme cristalline IV selon l'une quelconque des revendications 1 à 11.

FIG—1

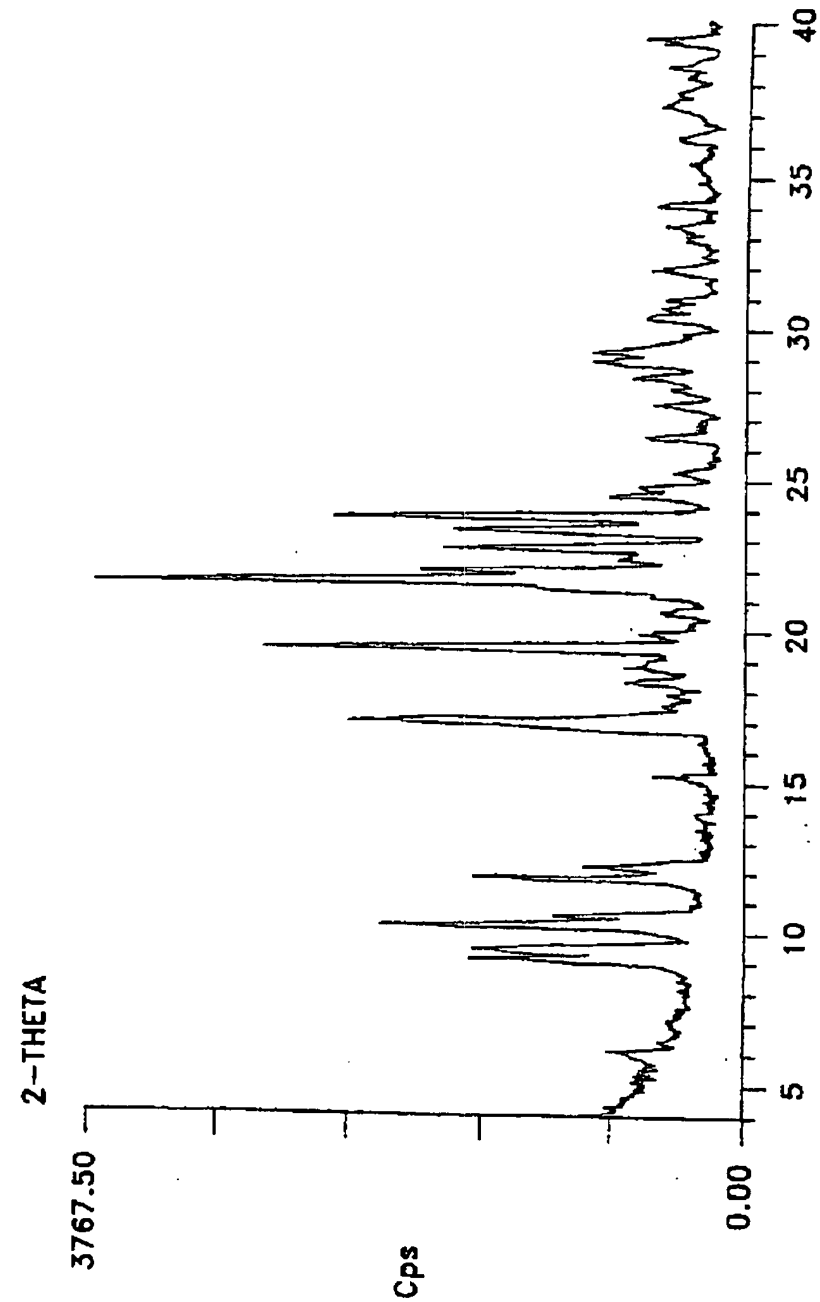
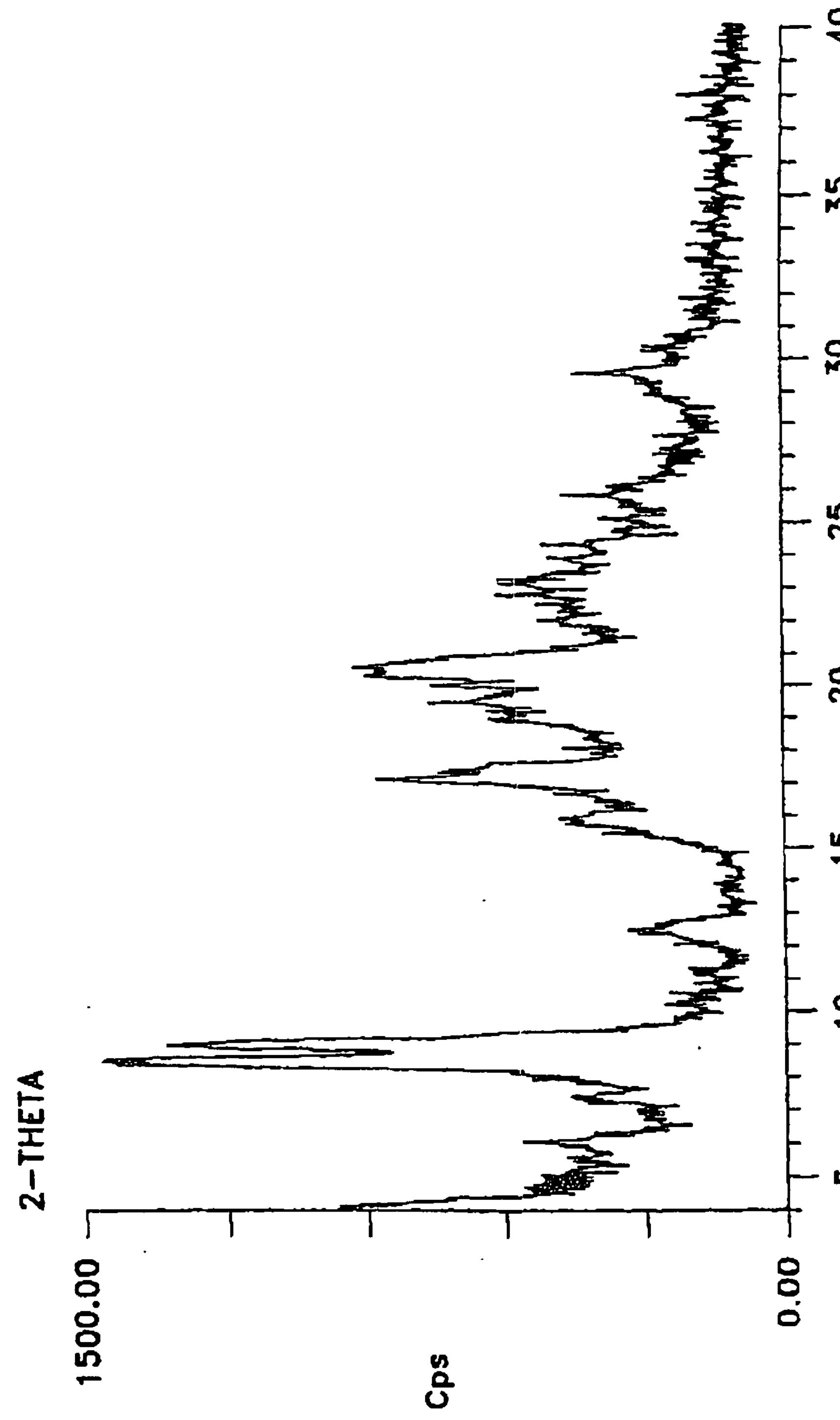
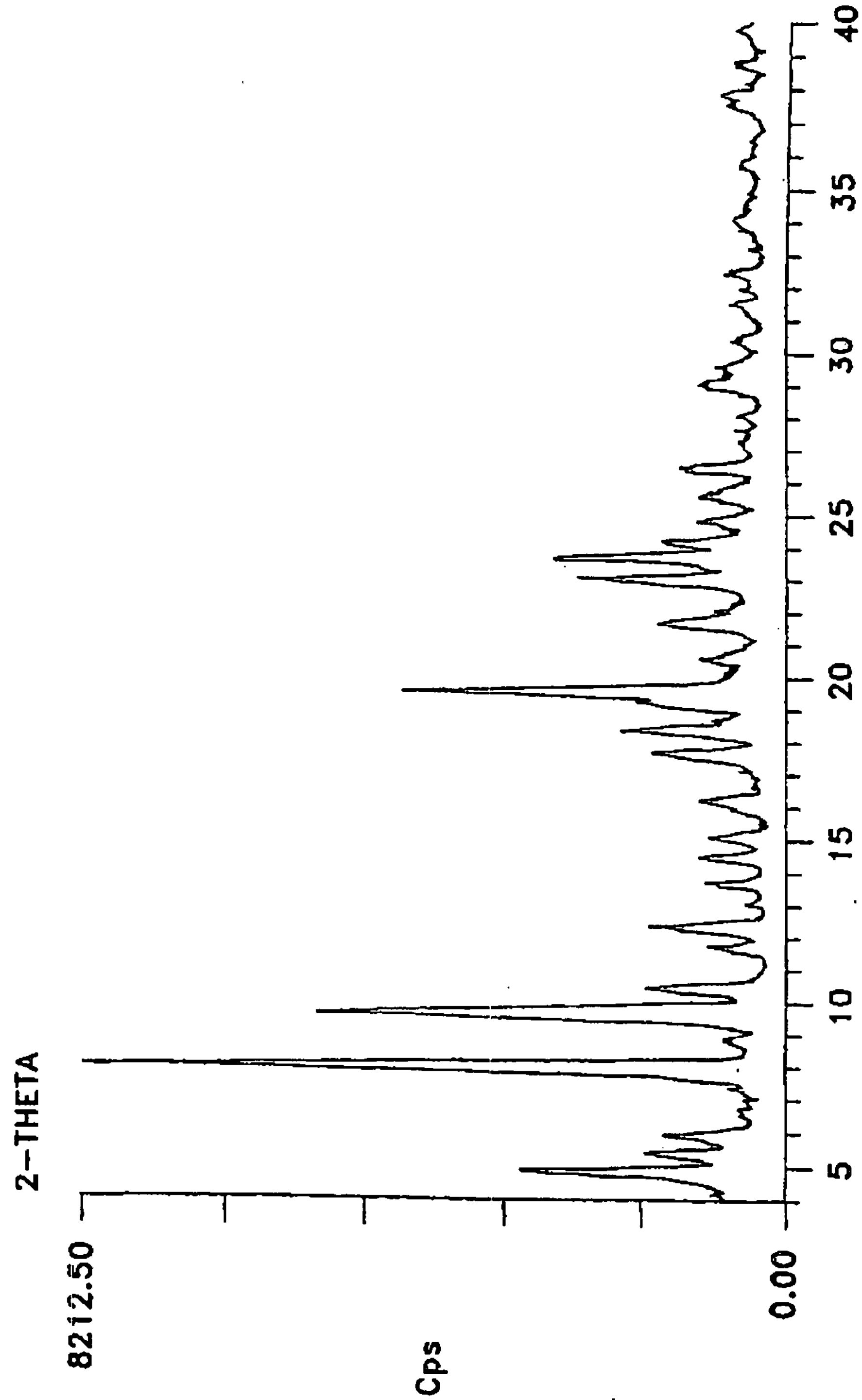


FIG-2



FIG—3



FIG—4